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REVIEW

Modulation of sodium channels as pharmacological tool for pain therapy—highlights and gaps

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Abstract

Voltage-gated sodium channels are crucially involved in the transduction and transmission of nociceptive signals and pathological pain states. In the past decades, a lot of effort has been spent examining and characterizing biophysical properties of the different sodium channels and their role in signaling pathways. Several gains of function mutations of the sodium channels Nav1.7, Nav1.8, and Nav1.9 are associated with pain disorders. Due to their critical role in nociceptive pathways voltage-gated sodium channels are regarded interesting targets for pharmacological pain treatment. However we still need to fill the gap that exists in the translation of efficacy in preclinical in vitro experiments and in models of pain into the clinic. This review summarizes biological and electrophysiological properties of voltage-gated sodium channels and aims to discuss limitations and promising pharmacological strategies in sodium channel research in the context of pain therapy.

Keywords Voltage-gated sodium channel · Analgesia · Pain signaling pathways · Translational research

Introduction

Over the last decades, a great amount of effort has been made to develop new pharmacological treatment strategies for pain management. There is urgent need for improved analgesic drugs since about 50% of patients with chronic pain show little or no response to current analgesic drug treatment (Breivik et al. 2006).

Voltage-gated sodium channels are important determinants of electrical excitability and have been extensively studied in the past three decades. So far more than 300 reviews have been published referring to the broad field of sodium channel research. Numerous preclinical studies demonstrate the involvement of voltage-gated sodium channels in the pathophysiology of pain states. Missense mutations of the sodium channels Nav1.7, Nav1.8, and Nav1.9 cause alterations in sodium channel function which result in enhanced repetitive firing and decreased action potential threshold thereby promoting hyperexcitability of nociceptive neurons (Waxman et al. 2014).

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This review gives an overview of structural and functional features of voltage-gated sodium channels and emphasizes the need for improved translational pain models.

Structure and classification of voltage-gated sodium channels

The alpha subunit represents the primary functional element of the sodium channel macromolecule consisting of approximately 1800 amino acids which are arranged in four homologous domains (Fig. 1). Each of the domains contains six alpha helical transmembrane segments. The alpha subunit harbors the voltage-sensor and the channel pore including the sodium selectivity filter. Most of the known pharmacological binding sites are located within the alpha subunit (Sula et al. 2017). Adjacent to the alpha subunit smaller (respectively 30–40 kDa) associated beta subunits encoded by the genes SCN1B–SCN4B modulate the channel's gating properties and contribute to stabilizing the channel protein within the plasma membrane (Namadurai et al. 2014). Due to their function as cell adhesion molecules, they are involved in cell migration during physiological processes such as the postnatal development of the CNS as well as pathological conditions like cancer metastasis (Brackenbury and Isom 2008).

Voltage-gated sodium channels can be pharmacologically classified as TTX-sensitive and TTX-"resistant": Due to the

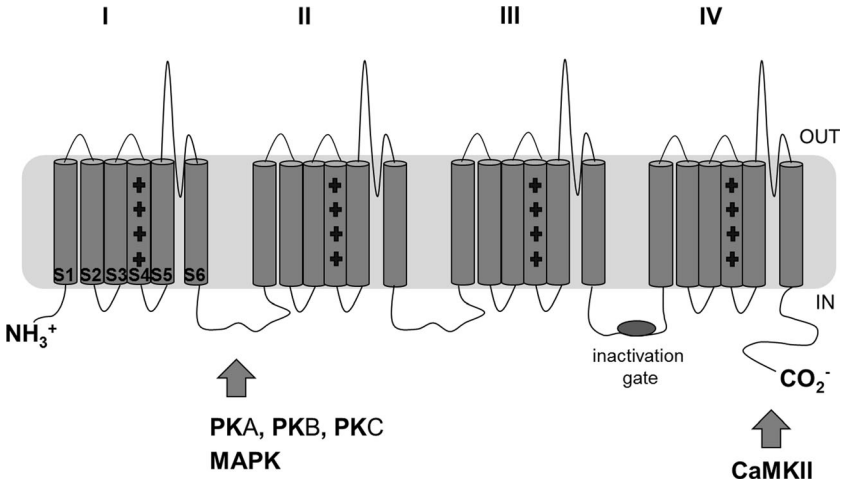

Fig. 1 Schematical illustration of the structure of the alpha subunit of voltage-gated sodium channels. Each of the four homologous domains (I–IV) contains six transmembrane segments. The ion channel pore is predominantly formed by the segments (S) 5 and 6. Positively charged amino acid residues in S4 constitute the primal voltage-sensing region. The intracellular loop connecting domains III and IV harbors the highly conserved amino acid sequence isoleucine, phenylalanine, and methionine (IFM) which mediates fast inactivation of the channel. The arrows indicate regions of the alpha subunit which contain phosphorylation sites of protein kinase A, B, and C (PKA, PKB, PKC), mitogen-activated protein kinase (MAPK), and calcium/calmodulin-dependent protein kinase II (CaMKII)

presence of the amino acids serine (Nav1.8 and Nav1.9) and cysteine (Nav1.5) within the linker between segments (S) 5 and S 6 the channels Nav1.5, Nav1.8, and Nav1.9 are not blocked by nanomolar, but more than 1 μM concentrations of tetrodotoxin (TTX) (thus named "TTX-resistant") while the other TTX-sensitive voltage-gated sodium channels harbor amino acid residues with an aromatic ring in the respective linker and are inhibited by low nanomolar concentrations of TTX (Cohen and Strichartz 1977; Yu and Catterall 2003; Leffler et al. 2005).

Nine identified genes (SCN1A–SCN5A and SCN8A–SCN11A) encode different voltage-gated sodium channels with a characteristic distribution throughout the body. Although the nine channels show about 50% homology regarding their primary sequence, their gating properties differ. The individual biophysical properties of the nine sodium channels and their varying expression among excitable membranes characterize the patterns of electrical activity in different tissues.

Due to their crucial role in pain pathophysiology, the biological and functional features of the voltage-gated sodium channels Nav1.7, Nav1.8, and Nav1.9 are described in detail hereinafter:

Nav1.7

Nav1.7 is abundantly expressed in nociceptive neurons and is also found in visceral and in olfactory sensory neurons; hypothalamic, sympathetic, and myenteric neurons; and in smooth muscle (Waxman 2007). By amplification of subthreshold depolarizations, Nav1.7 can trigger the generation of action potentials. Activation and inactivation of Nav1.7 show a fast kinetic while its recovery from fast inactivation is slow (Cummins et al. 1998). Several pain disorders such as inherited erythromelalgia (IEM), paroxysmal extreme pain disorder (PEPD), and idiopathic small fiber neuropathies are linked to Nav1.7 mutations (Cummins et al. 2004; Choi et al. 2011). PEPD mutations compromise inactivation of Nav1.7 while IEM mutations alter voltage dependence of activation resulting in channel activation at more hyperpolarized potentials. Nav1.7 has gained special interest since loss of function mutations of this channel induce a loss of pain perception denoted "congenital indifference to pain" (CIP) (Cox et al. 2006). Besides the inability to perceive pain and an impaired sense of smell or a complete anosmia, patients with CIP show no abnormal organic function (Goldberg et al. 2007; Weiss et al. 2011). Therefore, Nav1.7 is regarded a promising target for the development of sodium channel blockers which selectively modulate pain without exhibiting effects on other organs.

Nav1.8

Nav1.8 is highly expressed in small and medium nociceptive neurons as well as in myelinated afferent type A fibers and in cranial sensory ganglia (Shields et al. 2012). It is also present in intracardiac ganglia where its functional role needs to be further explored (Verkerk et al. 2012). It represents the main inward current during the upstroke of the action potential in dorsal root ganglion neurons and is a key determinant for transmission of (noxious) thermal, mechanical, and inflammatory stimuli (Akopian et al. 1999; Jarvis et al. 2007; Patrick

Harty and Waxman 2007; Zimmermann et al. 2007). Its kinetic properties, among others, its rather fast recovery from inactivation, support high frequency discharges (Han et al. 2015).

Nav1.9

This channel is predominantly expressed in DRG-neurons with a diameter smaller than 30 μm, in trigeminal neurons and in intrinsic neurons of the myenteric plexus (Dib-Hajj et al. 2002). Seven mutations of the gene SCN11A which encodes the Nav1.9 alpha subunit were found to cause peripheral neuropathy syndromes (Huang et al. 2014). Nav1.9 already activates at hyperpolarized potentials (around − 60 mV) (Herzog et al. 2001). Due to its slow and incomplete inactivation, it generates a persistent sodium current enabling plateau potentials and repetitive depolarizations (Coste et al. 2004). With a homology of about 45%, the primary structure of the alpha subunit of the Nav1.9 channel differs the most compared to the other eight voltage-gated sodium channels (Dib-Hajj et al. 1998; Dib-Hajj et al. 2015). The less conserved structure can be a favorable condition to develop Nav1.9-selective blockers.

To examine Nav1.9 currents in vitro is challenging due to difficulties in expression of Nav1.9 channels in heterologous systems and a rundown of Nav1.9 current in the course of electrophysiological experiments (Leffler et al. 2005; Goral et al. 2015). Protein engineering approaches like the use of voltage-activated potassium channels into which isolated voltage-sensing paddle motifs of the Nav1.9 alpha subunit are "transplanted" help to bridge these obstacles. It needs to be further evaluated to what degree the functional properties of Nav1.9 channels can be characterized by such chimeric constructs (Bosmans et al. 2011).

Modification of voltage-gated sodium channels

Sodium channels are macromolecular complexes which are modulated by several pathways of cellular signal transduction and interact with numerous other proteins (Wood et al. 2004; Laedermann et al. 2015). Sodium channel function, expression, and distribution patterns are altered in the course of pathological processes like inflammation, metabolic disorders, or nerve injury resulting in characteristic changes in membrane excitability. Nociceptive and inflammatory mediators such as bradykinin, serotonin, adenosine, histamine, prostaglandin E2, epinephrine, endothelin-1, and nerve growth factor induce either changes in sodium channel gating and/or channel trafficking (Woolf et al. 1994; Rush and Waxman 2004; Vanoye et al. 2013; Leo et al. 2015). Different enzymes, among others protein kinase A, B, and C, mitogen-activated protein kinase, and calcium/calmodulin-dependent protein kinase II induce posttranslational modifications of voltage-gated sodium channels culminating in short- and long-term alteration of sodium inward currents (Fig. 1) (Laedermann et al. 2015). Several pathways of posttranslational modification are discussed to contribute to pathological pain states and the transition from acute to chronic pain (for further review see Scheuer 2011; Laedermann et al. 2015). It is not yet fully resolved to what degree these modifications translate to actual changes in excitability (Bhave and Gereau 4th 2004).

Furthermore, epigenetic modifications contribute to long-term alterations of sodium channel expression. miR-7a down-regulation has been demonstrated to increase sodium channel β2 subunit protein expression and was associated with increased pain in the late phase of a rat model of neuropathic pain (Sakai et al. 2013). Manipulating selected miRNA proved successful in alleviating pain in preclinical studies. Using the chronic constriction injury model, miR-96 mRNA expression in rat dorsal root ganglion neurons was downregulated after sciatic nerve ligation while expression of the Nav1.3 channels increased. During daily intrathecal injections of miR-96, the mRNA and protein level of Nav1.3 could be restored. These alterations where accompanied by a reduction of tactile hypersensitivity/allodynia (Chen et al. 2014). Further research is warranted to elucidate the clinical impact of epigenetic modifications of voltage-gated sodium channels on chronic pain.

Another yet not completely understood aspect which might further be taken into account is the correlation between channel gating and an intrinsic property termed long-term memory. The sequence of channel opening and closing can influence channel behavior similar to a regulatory self-tuning feedback loop (Liebovitch and Todorov 1996; Wawrzkiewicz et al. 2012; Qin 2014; Law and Levin 2015). The influence of this bioelectric process in pathological conditions such as chronic pain has not yet been examined. One challenge of future research is to establish methodological approaches by which the influence of-long term dynamic changes of sodium channel kinetics on neuronal plasticity can be analyzed in detail.

Preferential inhibition of pathological electrical activity

Changes in membrane potential induce complex conformational changes of sodium channels which have not yet been completely understood in detail. Upon depolarization, the channels open within a fraction of a millisecond. Within a few milliseconds, a rapid/fast inactivation occurs which limits current flow and thereby terminates the depolarizing phase of the action potential. Prolonged or recurrent depolarizations induce other non-conducting states subsumed under the term slow inactivation. The detailed kinetic properties of slow inactivation are still under investigation. Slow inactivation is involved in physiological processes such as neuronal plasticity and pathological conditions, for example, periodic paralysis (Silva 2014).

Among the many sodium channel modulating agents, each compound has characteristic binding affinities for the different conformational states of the channel. As an example, mexiletine preferentially blocks the open state of the channel while tetrodotoxin and also saxitoxin bind to different conformational states with almost the same affinity (Pal and Gangopadhyay 2015). Even structurally very similar compounds show different patterns in terms of modulation of the various conformational states (Haeseler et al. 2001; King et al. 2012). A functional selectivity can be given by a different affinity of a sodium channel modulator to the diverse channel states. As a characteristic local anesthetic like molecular action, a great number of nonselective sodium channel blockers exert membrane stabilizing effects by preferential inhibition of inactivated channels (Nau and Wang 2004). Drugs which selectively block hyperexcitable nerves/ectopic activity while leaving physiological nerve conduction unchanged would be ideal candidates in terms of an improved therapeutic utility. The functional selectivity, i.e., the state-and frequency dependent block of voltage-gated sodium channels by a number of non-selective sodium channel inhibitors such as several anticonvulsants and antidepressants is regarded to reduce adverse effects.

Another pharmacological strategy for a differentiated inhibition of pain pathways is the targeted application of molecules—such as QX-314, a membrane-impermeable lidocaine derivative (Binshtok et al. 2009)—to selectively modulate ion channel signaling in nociceptive neurons. A deeper understanding of the interplay of voltage-gated sodium channels and transient receptor potential (TRP) channels can facilitate the development of further molecular approaches for targeted inhibition of pathological electrical activity (Stueber et al. 2016).

Besides the regular transient sodium current in a subset of central and peripheral neurons characteristic, sodium inward currents are present which can promote repetitive action potential firing in neurons (Enomoto et al. 2018). The function and role of current components such as the resurgent current or persistent current have not yet been fully examined. Resurgent currents as well as persistent currents are involved in several pathological conditions such as epileptic disorders and syndromes associated with genetically driven sodium channelopathies like paramyotonia congenita and the paroxysmal extreme pain disorder (Kiss 2008; Lewis and Raman 2014; Jarecki et al. 2010). Resurgent currents in dorsal root ganglion neurons are enhanced by inflammatory mediators (Tan et al. 2014). Persistent and resurgent currents are interesting targets for the development of new analgesic sodium channel blockers. Particularly in the field of development of antiarrhythmic agents, several molecules have been identified as potent blockers of persistent currents (Camm 2017). However, the knowledge about the clinical effectiveness of selective inhibitors of the persistent sodium current is still limited (Heijman et al. 2017).

Resurgent currents are suppressed by low micromolar concentrations of the endogenous cannabinoid anandamide (Theile and Cummins 2011) and the synthetic cannabinoid ajulemic acid (AJA) (Fig. 2) (Foadi et al. 2014). The molecular determinants of selective suppression of resurgent currents need to be further explored. Further insights into the interaction of the onset of resurgent current and the process of channel inactivation might provide a molecular basis for the development of selective resurgent current inhibitors. In this context, cannabinoids like anandamide and AJA might be promising lead compounds.

From the methodological point of view, progress in developing high-throughput electrophysiology platforms helped to accelerate the detection of potent sodium channel blocking molecules (Castle et al. 2009). Suitable electrophysiological protocols are needed for example to differentiate slow inactivation from slow unbinding of a drug from (fast) inactivated channels (Jo and Bean 2017). Besides, it is challenging to investigate the impact of drug binding on channel gating. Advancements of techniques of single channel patch clamp recording and of thermodynamic models can be useful to depict these multifactorial interactions (Armstrong 2006; Pal and Gangopadhyay 2015). But what is still missing is the analysis of clinical significance of investigated electrophysiological alterations. Up to now, we can hardly assess which in vitro methods can predict the clinical benefit of an investigated sodium channel blocker. Thus, more emphasis should be put on the development of experimental models which help to improve the predictive value of basic research results (Bagal et al. 2015).

The future challenge: bridging basic and clinical pain research

Drug promiscuity entails that almost every fourth pharmaceutical compound exerts a prominent inhibition of voltage-gated sodium channels in addition to having several other mechanisms of action (Lenkey et al. 2010). Although plenty of preclinical studies discovered potent sodium channel blockers whose molecular characteristics classified them as drugs with a promising antinociceptive profile, in relative terms rather few sodium channel modulators have been reported to have entered clinical trials, and in several clinical studies sodium channel blockers failed to reproduce robust analgesic effects (Bagal et al. 2015).

Coanalgetics like anticonvulsants and antidepressants are used in chronic pain states for several decades. Though several studies demonstrated sodium channel modulating effects of these drugs, the impact of sodium channel block on clinical analgesia has not yet been systematically analyzed. There is not enough evidence to what degree the pharmacological block of sodium channels translates to a clinical analgesic effect. Amitriptyline, for example, is recommended as a first

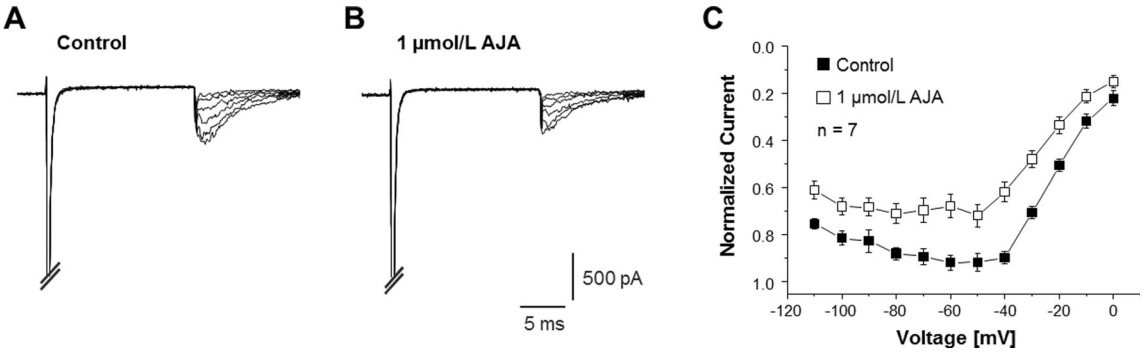

Fig. 2 Ajulemic acid (AJA) inhibits resurgent Nav1.5 currents. **a**, **b**. Typical current traces of Navβ4-peptide-mediated resurgent currents on Nav1.5 in control solution (**a**) and in presence of 1 µmol/L ajulemic acid (AJA) (**b**). Resurgent currents were induced by inclusion of 100 µmol/L Navβ4 peptide in the intracellular solution and elicited by 100-millisecond long hyperpolarizing test pulses ranging from 0 to − 110 mV following a 20 ms depolarizing pulse to + 30 mV. **c** Voltage-dependency of Navβ4-peptide-mediated resurgent currents activated as described above. Currents were normalized to the peak current amplitude in the respective control recording and plotted against the test pulse potential. Lines are drawn to guide the eye. Original source: Foadi et al. (2014) Inhibition of voltage-gated Na^+ channels by the synthetic cannabinoid ajulemic acid. Anesth Analg 118(6):1238–1245. (Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer. Please contact permissions@lww.com for further information)

line treatment for neuropathic pain (Moore et al. 2015). A number of preclinical and clinical studies demonstrate antinociceptive effects of amitriptyline. Similar to many other potent sodium channel blockers, the pharmacological actions of amitriptyline include a broad range of molecular targets such as the inhibition of norepinephrine and serotonin reuptake, modulation of sodium, calcium, and potassium channels (Mika et al. 2013). Our understanding of the interactions contributing to its therapeutic profile is still limited. Analgesic effects due to topical application of amitriptyline in animal models of pain and in preliminary clinical studies implicate that sodium channel block might have a clinically relevant impact on the antinociceptive profile of amitriptyline (Khan et al. 2002; Moghadamnia et al. 2009). But in the case of neuropathic pain, controlled clinical trials could not demonstrate a robust analgesic action of topical amitriptyline as depicted by a systematic review (Thompson and Brooks 2015). As highlighted below, there is need for improved experimental models to fill the translational gap between preclinical results and clinical therapeutic efficacy.

A number of aspects can limit the reliability of preclinical pain models: Challenging inconsistent results can arise from methodological and species-related differences. For instance the expression of Nav1.7 differs between mouse and human dorsal root ganglion neurons (Chang et al. 2017). As another example in a rat model of spinal contusion injury, antisense knockdown of Nav1.3 has been shown to be associated with an alleviation of hyperexcitability and decreased pain-related behavior (Hains et al. 2003). However Nav1.3 knock-out mice developed characteristic patterns of neuropathic pain and an unaltered pain behavior after spinal nerve ligation (Nassar et al. 2006). Neuroanatomical differences between rats, mice, and humans, for example, regarding the pathway to the forebrain that is crucial for pain sensation in humans (Craig et al. 2002), can cause different outcomes in pain end points. In experimental models of pain, it is difficult to reliably capture alterations which show temporal dynamic, for example, most of the animal pain models focus on acute inflammatory states (Tan et al. 2014) or do not make allowance for spontaneous pain, which in humans is a very prominent symptom, especially of neuropathic pain (Krishnan et al. 2009). In several studies on animal pain models, withdrawal reflexes were assessed as sole outcome measure which does not suit the complexity of pain states in humans (Rice et al. 2008).

Research around voltage-gated sodium channels impressively demonstrates the translational gap and the challenging aspects of pain research: Insensitivity to pain has been regarded a phenotypic attribute of human Nav1.7 null subjects. But still affected humans as well as Nav1.7 knock-out mice can develop neuropathic pain (Nassar et al. 2004; Wheeler et al. 2015). It has been shown that in order to gain the hypoalgesic phenotype of Nav1.7 null subjects, a 100% antagonism of Nav1.7 channels is needed which is hardly possible to achieve by one compound (Emery et al. 2016). The monoclonal antibody SVmab, a selective Nav1.7 inhibitor, exhibits analgesic and anti-pruritic effects in different mouse models of nociception (Lee et al. 2014). Its recombinant analog, rSVmab, has a much lower binding affinity for Nav1.7 in human embryonic kidney cells, human nerve tissue, and mouse DRG neurons compared to Svmab, but still rSVmab exerts analgesic effects in the murine paclitaxel-induced neuropathic pain model (Bang et al. 2018). The molecular mechanisms of this action yet remain unclear.

Recent studies provided a deeper understanding of the relation of sodium inward currents to other signaling pathways: Minett et al. elucidated, that the precursor of met-enkephalin,

an endogenous opioid peptide, is upregulated in human Nav1.7 null subjects and in Nav1.7 knock-out mice. Thus, sodium seems to represent a second messenger which modifies the expression of endogenous opioid peptides (Minett et al. 2015). This is accompanied by a decrease in pronociceptive serotonergic signals in Nav1.7 knock-out mice (Isensee et al. 2017).

Progress is underway regarding promising experimental models which help to bridge the translational gap (Bulmer and Grundy 2011). Among others, the conversion of pluripotent stem cells into nociceptors (Chambers et al. 2012), the development of human neuron-glia test systems (Luongo et al. 2014), and improved human pain models (Lötsch et al. 2014) are examples for translational approaches to shed further light on the complex, and still not clearly revealed pathomechanisms of pain states.

Conclusion

Sodium channels constitute relevant pharmacological targets. Sodium channel blocking agents are used in the treatment of pain states, arrhythmias, epileptic syndromes, and neurodegenerative diseases. Studies investigating the interaction of sodium channel function with different players of the molecular "pain network" using translational approaches can broaden our knowledge regarding the influence of sodium channel modulation on clinical analgesia. Future research should give more emphasis to establish preclinical pain models which provide superior predictive validity. This would improve the efficacy of screening of novel sodium channel modulators. In parallel with the use of advanced translational techniques, an increased systematical interchange and cooperation of basic and clinical researchers can be helpful to reduce gaps between in vitro, in vivo, and clinical studies.

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